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WILL RADIATION-INDUCED BYSTANDER EFFECTS OR ADAPTIVE RESPONSES IMPACT ON THE SHAPE OF THE DOSE RESPONSE RELATIONSHIPS AT LOW DOSES OF IONIZING RADIATION?

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□ Radiation induced bystander effects and adaptive responses are two phenomena that modulate cellular responses to low doses of ionizing radiation. Bystander effects generally exaggerate the effects of low doses of radiation by eliciting detrimental effects in non-irradiated cells, thus making the target for radiation effects greater than the volume irradiated. Adaptive responses on the other hand indicate that low doses of radiation can reduce damage induced by a second challenging dose. The potential impact of these two low dose effects on the shape of the dose response relationship will be discussed.

I. INTRODUCTION

There is no question that exposure to ionizing radiation can cause cancer but a qualitative relationship between cancer induction and exposure to low doses of radiation (<10cGy) is equivocal and controversial. Analysis of the cancer incidence among Japanese A-bomb survivors suggests that for solid tumors the dose response relationship is a linear function of dose between 10 and 250cGy [1]. At present, cancer risks at doses lower than those for which direct epidemiological observations are available are obtained by a linear extrapolation from these higher doses [2]. There are a number of low dose phenomena that might modulate the biological effects at doses less than 10cGy such that a linear extrapolation might not truly reflect low dose risk. These include radiation induced bystander effects (BSEs), adaptive responses (ARs), and potential radiation sensitive sub-groups in the human population. In this manuscript I will consider how two of these low dose phenomena, BSEs and ARs might impact on the shape of the dose response relationship at low doses of ionizing radiation. Thanks largely to a research program initiated by the US Department of Energy (http://lowdose.tricity.wsu.edu) considerable attention has recently been focused on biological effects occurring after exposure to low doses of radiation (<10cGy). Two targeted research areas are BSEs and ARs.

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II. BYSTANDER EFFECTS

BSEs refer to those effects occurring in cells that were not "hit" i.e., traversed by an ionizing particle, but were neighbors of cells that were irradiated. These cells might have been in the same radiation environment or they might be non-irradiated cells that received culture medium from irradiated cells. Many, but not all, BSEs described to date are detrimental to the bystander cell and these include induced mutations, chromosomal rearrangements, micronuclei, transformation and/or cell killing (reviewed in [3,4]). Both cell-to-cell gap junction communication and the production of soluble factors by irradiated cells have been implicated mechanistically in BSE (reviewed in [3]), but the nature of the bystander factor remains to be determined. BSEs appear to be largely a low-dose phenomena [5,6] and like most biological systems there is considerable variability in an individual's ability to elicit and/or respond to a bystander signal [7].

III. ADAPTIVE RESPONSES

ARs refer to the phenomenon by which cells irradiated with a low "priming" or "adapting" dose of ionizing radiation, generally less that 10cGy, become refractory to the genotoxic effect of a subsequent challenge with a high dose of radiation (>100cGy). First reported in mammalian cells by Olivieri et al. [8] who pretreated human lymphocytes with low doses of radioactive thymidine and found that these pretreated cells showed significantly lower frequencies of chromatid aberrations upon subsequent exposure to a challenge dose of 150cGy compared with non-primed cells. Since then, there have been numerous reports demonstrating the presence of AR response in a variety of mammalian cells using endpoints such as chromosomal aberrations [8-11], micronuclei formation [12,13], mutation induction and spectrum [14,15], neoplastic transformation [16,17], apoptosis [18,19], cell proliferation [20], and cell killing [21]. It should be stressed that there is considerable variability in the degree of response in both *in vitro* cell culture systems and within and between individuals in *in vivo* studies [22,23]. There is evidence that the AR is modulated by dose rate [24], and the phenomenon cannot be adequately explained by the presence of a sensitive subpopulation of cells [10,11,25]. ARs have also been described *in vivo* after clinical, environmental or occupational exposure to radiation [12,26-31].

A molecular mechanism for the AR has not yet been described, but there is evidence that gene transcription and/or protein synthesis is required, and that proteins involved in cellular signaling and DNA repair are linked to the process [32-37]. In addition, the induction of early response genes [38,39] as well as changes in gene expression [40] resulting in a cascade of protein-DNA interactions that regulate gene transcription has also been proposed to explain the AR.

IV. IMPACT UPON DOSE RESPONSE RELATIONSHIPS

As such BSE and AR appear to be two conflicting low dose phenomena. BSE generally exaggerate the effects of low doses of radiation by eliciting detrimental effects in non-irradiated cells, thus making the target for radiation effects greater than the volume irradiated. ARs indicate that low doses of radiation can reduce damage induced by a second challenging dose. Consequently BSE and AR have the potential to impact on the shape of the dose response profile at low doses of radiation (Figure 1).

In a recent study, Zhou *et al.* [41] have investigated the interaction between a specific BSE and an AR. Interestingly, they found that a low adapting dose of radiation decreased bystander-mediated mutagenesis in human hamster A_L cells. Thus, the AR decreases non-targeted bystander mutagenesis. However bystander cells show an increase in sensitivity after a subsequent challenge with X-rays [41]. Zhou and colleagues concluded that radiobiological responses at low radiation doses are likely to be a complex interplay among directly induced radiation effects, BSE and AR's. This is a logical and reasonable conclusion.

However, it is not immediately obvious how an AR will impact on radiation risk unless the "adapted" cell, organ, tissue, or individual is exposed to a subsequent challenge with a higher dose of radiation. This is an unlikely scenario for the population at large. Furthermore, AR studies are usually done with a finite period of time between the adapting and chal-

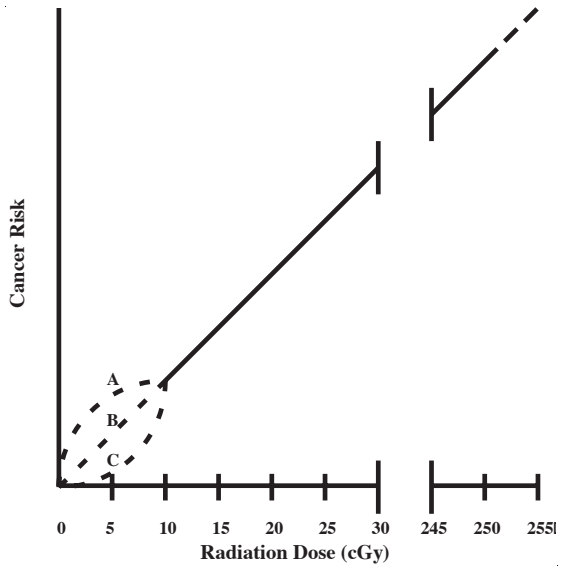

FIGURE 1. A hypothetical schematic for extrapolating risk evaluated at a given biological endpoint as a function of radiation dose. A. How BSEs might impact on extrapolation from a high dose to a low dose. B. Linear extrapolation as currently recommended by regulatory bodies. C. How ARs might impact on extrapolation from a high dose to a low dose.

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lenging doses, usually four to six hours. While detailed information documenting the lifetime of the radiation induced AR *in vivo* is yet to be provided, it is probable that like other aspects of the AR this will be highly variable in the human population [29-31]. Nevertheless, there may be specific examples when both BSE and AR apply. For example, among underground miners and individuals living in high radon areas, the interacting effect between the two phenomena cannot be totally discounted. The evidence for bystander effects is indisputable (reviewed in [3,4]) and recent studies documenting a related radiation induced abscopal effect *in vivo* [42,43] lend credence to the significance of non-targeted effects in animal model systems. Consequently, it is this author's thesis that while BSEs and ARs have the potential to impact on the shape of the dose relationship after low doses of radiation, it would be premature to either overestimate or underestimate this impact until we understand the nature of the bystander factor and the biological significance of the BSE *in vivo*.

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